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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/680,386

10/07/2003

Richard Kolodner

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EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT

PAPER NUMBER

1637

DATE MAILED: 05/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/680,386

Applicant(s)

KOLODNER ET AL.

Examiner

Jeffrey Fredman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 13-38 is/are pending in the application.
- 4a) Of the above claim(s) 1 and 38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) ☐ Notice of Informal Patent Application (PTO-152) |
| 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>10/07/03</u> . | 6) ☐ Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group III, claims 13-37 in the reply filed on April 17, 2006 is acknowledged. Claims 1 and 38 are withdrawn from further consideration.

Claim Rejections - 35 USC § 112 – Written Description

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 13-26 and 28-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

The current claims are drawn to identification of "alterations" in the human "MSH5" gene. Claims associate these alterations with "predisposition to malignant growth" (see claim 16); "predisposition to inappropriate meiotic segregation" (see claim 17); "diagnosing a tumor" (see claim 33) and "prognosis of cancer" (see claim 36). However, no specific wild type sequence is required by any of the claims other than claim 27 (which is not included in this rejection). The comparison is solely with an "MSH5" gene with no specific sequence required as a control.

The specification does not identify a single alteration. There is no description of any alteration, polymorphism, allele, mutation or change in the human MSH5 gene in the specification. The specification does not provide any association of any alteration with any disease state including cancer, tumors, malignancy of any sort or meiotic segregation. This disclosure does not provide description for all possible polymorphisms in SEQ ID NO: 1 which may be associated with cancer, tumors, malignancy of any sort or meiotic segregation.

All of the current claims encompass a genus of nucleic acids which comprise mammalian MSH5 polymorphisms which are not disclosed in the specification. The genus includes an enormous number of polymorphisms for which no written description is provided in the specification. This large genus is represented in the specification by zero polymorphisms. Thus, applicant has express possession of zero particular polymorphisms, in a genus which comprises hundreds of trillions of different possibilities. Here, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. No structural limitations

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or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with cancer, tumors, malignancy of any sort or meiotic segregation is provided. Further, these claims expressly encompass all the different possible allelic variants including insertions, deletion, substitutions and transversions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing additional sequence, which are associated with any phenotype are described in the specification.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

"A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition in claim 13 of a polymorphism lacks any specific structure. The further requirement in dependent claims for alterations associated with cancer, tumors, malignancy of any sort or meiotic segregation are even more lacking in associated structure. These claims represent precisely the situation of naming a type of material which is generally known to likely exist, polymorphisms in the MSH5 gene but are in the absence of knowledge of the material composition and fails to provide

descriptive support for the generic claim to "a polymorphism in the MSH5 gene", for example.

In particular, the claims also encompass any mammalian genome. So the claims as currently written are not limited to polymorphisms in the human MSH5 gene, but are inclusive of mutations in the bat, whale, fossa, gerbil and horse genes as well. This broad and unsupported claim lacks even a single human polymorphism that has any association, much less other mammalian polymorphisms.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

"...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely by its functional utility, without any structural definition of the particular polymorphisms claimed. This is necessary because the specification lacks any structural definition of any polymorphisms in humans or in any other mammalian species. The specification provides only a particular sequence for the human MSH5 gene.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

"...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise polymorphisms of the human MSH5 genes. Another issue is whether there is any structure function relationship which correlates the function, cancer, tumors, malignancy of any sort or meiotic segregation, with a particular structure. This question fundamentally addresses the issue of whether there is any structure which the specification demonstrates is necessarily correlated with the function of cancer, tumors, malignancy of any sort or meiotic segregation. In this case, the answer is no, there is no structure given whatsoever, which is shown, suggested, or otherwise indicated as associated with cancer, tumors, malignancy of any sort or meiotic segregation.

Conceptually, at minimum a polymorphism is a single nucleotide change in a DNA sequence. It may represent a larger change, including a deletion, an insertion or multiple changes, but minimally consists of a single nucleotide change. To describe such a change, both possible nucleotides at the position of interest must be disclosed. It is insufficient to describe a polymorphism as, hypothetically, an Adenine at position 57, because this is not a polymorphism, just a sequence. In order to be a polymorphism, the description must state, for example, a Guanosine for Adenine change at position 57. So the description of a sequence is not a description of a polymorphism, since the sequence alone does not provide the structure of the change that IS the polymorphism. Therefore, the disclosure of SEQ ID NO: 1 is not a description of any alterations but simply the disclosure of a sequence. Therefore, the

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claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Claim Rejections - 35 USC § 112 – Scope of Enablement

4. Claims 13-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention

The claims are drawn to polymorphisms in the MSH5 gene. Some of the dependent claims associate the polymorphisms with cancer, tumors, malignancy of any sort or meiotic segregation. The invention is is the class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are broadly drawn to encompass any polymorphism in a mammalian sequence named MSH5. Even the narrowest claim is drawn to any polymorphism in a sequence comprising SEQ ID NO: 1. The claims broadly encompasses the polymorphisms in any mammalian patient. This means that the method is broadly drawn to the use, not only of human polymorphisms, but also of sheep, bats, whales, voles, fossa, gerbil, horse or any other mammal. Further, the animals undergoing the screening may contain any of a number of complicating variables, since the background genotype with regard to other genes may play significant roles in the effect on cancer, tumors, malignancy of any sort or meiotic segregation.

Quantity of Experimentation

The quantity of experimentation in this area is very large since there is significant variability in the effects of polymorphisms on phenotypes such as cancer, tumors, malignancy of any sort or meiotic segregation. Screening each possible polymorphism in the MSH5 genes represents an inventive, unpredictable and difficult undertaking in itself. In human studies alone, this would require years of inventive effort, with each of the many intervening steps to analyze the impact, prognostic efficacy and diagnostic impact of particular MSH5 mutations. There would not be any guarantee of success in the succeeding steps.

Wacholder et al (J. Natl. Cancer Institute (2004) 96(6):434-442) notes with regard to association of mutations studies that larger studies with 1500 participants have significantly more statistical power than smaller studies (see page 435). So the quantity

of experimentation factor supports the conclusion that a large quantity of experimentation, with the use of many hundreds, perhaps even thousands, of patient samples would be necessary to demonstrate an association for polymorphisms. This is a very large amount of experimentation.

The unpredictability of the art and the state of the prior art

The art is replete with evidence that gene association studies are typically wrong. In fact, Lucentini et al (The Scientist (2004) Vol 18) titled his article "Gene Association Studies Typically Wrong" and states "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding (see page 2 of printout)." This is consistent with the teaching of Wacholder et al (J. Natl. Cancer Institute (2004) 96(6):434-442) who notes that "Too many reports of associations between genetic variants and common cancer sites and other complex diseases are false positives (see abstract). Ioannidis (Nature genetics (2001) 29:306-309) further supports this conclusion in pointing out the heterogeneity of results among different studies of genetic polymorphisms (see abstract, for example).

The art specifically drawn to MSH5 strongly demonstrates this unpredictability. Yi et al (Biochem. Biophys. Res. Comm. (2005) 332:524-532) in 2005 states "Apparently, a full appreciation of hMSH5 P29S in humans awaits clarification of the functions of hMSH5 as well as the molecular composition of hMSH5 associated protein complex. This line of research is presently on going in our laboratory (see page 532, column 1)." So years after the filing date, the art has identified a mutation in MSH5, but

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has no idea of the biological role of MSH5 itself, and even less of an idea of how the alteration affects MSH5 function.

One common problem in associated alleles with particular diseases is that the gene may have no role in the disease at issue, but may be, in some patients, in linkage disequilibrium with the true disease gene. Hung et al (Proc. Natl. Acad. Sci. (2005) 102(11):4134-4139) illustrates this problem in showing that an allele of hMSH5 is associated adverse reactions to allopurinol (see page 4137, column 1), along with several other genes including BAT3 and MICB. This showing does not demonstrate that hMSH5 is itself associated with these adverse reactions, but rather shows that polymorphisms may have associations which are entirely unpredictable. Certainly, the current specification does not predict any association of allopurinol adverse reactions with MSH5 alleles, but the claim is drawn to encompass such analysis methods.

Therefore, it is highly unpredictable whether some currently unknown polymorphism in the MSH5 gene would have any association with any disease, much less cancer, tumors, malignancy of any sort or meiotic segregation.

Working Examples

The specification has a working example where two polymorphisms are associated with hypercholesterolemia.

Guidance in the Specification.

The specification did not provide sufficiency evidence to demonstrate the association of any polymorphism in SEQ ID NO: 1 with cancer, tumors, malignancy of

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any sort, meiotic segregation or any other disease. The specification entirely lacks any teaching or discussion of MSH5 polymorphisms.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching gene association studies are highly unpredictable is demonstrated by Lucentini, Wacholder and Ioannidis. The specification provides one with no written description or guidance that leads one to a reliable method where any polymorphisms will be associated with anything whatsoever, much less a disease such as cancer, tumors, malignancy of any sort or meiotic segregation. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Further the specification does not provide guidance to overcome art and specification recognized problems in the use of polymorphisms as diagnostic of cancer, tumors, malignancy of any sort or meiotic segregation as broadly claimed. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the complete absence of any working examples and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would

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require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Jeffrey Fredman
Primary Examiner
Art Unit 1637

5/18/06